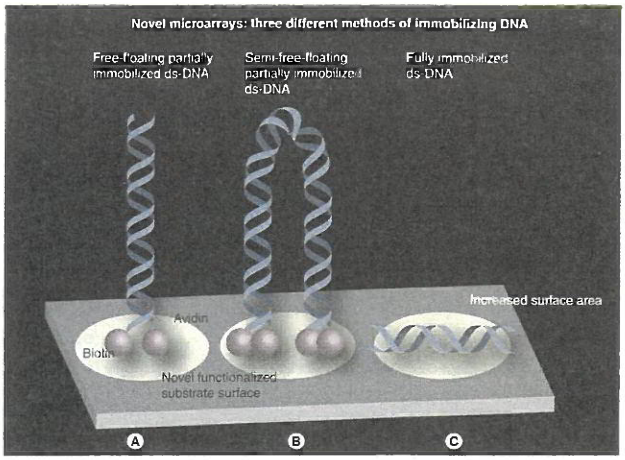
DNA Microarray Technology for Pharmacogenomics Research

Claude E. Gagna, PhD
Assistant Professor
Director of Biology Laboratories
New York Institute of Technologies
New York
W. Clark Lambert, MD, PhD
Professor
Department of Pathology
Department of Medicine
New Jersey Medical School
Newark, N.J.
Peter Lambert
Medical Student
St. Georges University School of Medicine
St. Georges, Grenada

Microarrays are a collection of DNA sequences that are immobilized onto a solid support. Microarrays—along with pharmacogenomics—are playing a significant role in the genomics and proteomics revolution. DNA and RNA are now viewed as dynamic molecules that can undergo structural changes. An example of this is the more conventional dsB-DNA transitioning itself to the alternative Z-DNA conformation. Z-DNA is an alternative form of B-DNA in which the double helix unwinds to the left instead of the right.

Exotic structural transitions can also occur in RNA. Gene expression is regulated by the DNA base pairs, nucleic acid-binding proteins, and structural changes that occur in dsDNA. Native zones of DNA in genes are elastic enough to allow for major structural changes that maximize stacking factors while decreasing disapproving steric interactions. The effects of local DNA supercoiling fashioned by transcription can stabilize alternative DNA structures, such as Z-DNA. Nucleic acids can assume many other unusual structures as well, meaning that the description of nucleic acid base pairs, distribution, and content alone does not offer investigators enough understanding of the factors that control gene expression. With the aim of more fully studying gene expression and discovering new DNA and RNA target sites for pharmaceuticals, scientists must focus more on the characterization of exotic double stranded and single-stranded (ss) nucleic acid structures, multistranded nucleic acids, and potential DNA and RNA sequences that undergo significant structural changes.

Pharmacogenomics must progress outside its current limitations (e.g., base pairs) and include alternative and multistranded nucleic acids, and structural transitions occurring within nucleic acids. The targeting of structural changes in genes and proteins, due to post-translational adjustments, increases scientists' knowledge of gene expression.



This figure reveals how different nucleic acids can be immobilized to a solid support: (A) quadruplex DNA, (B) triplex DNA, and (C) double-stranded (ds-) DNA. The nucleic acids can be tested for their ability to bind with drugs and/or proteins under different conditions, and for structural transitions. (Source: *Pharmacogenomics*[1])

Conventional nucleic acid-based microarrays have been employed to identify changes in the expression of genes, to isolate specific DNA or RNA sequences, and in location analysis of DNA molecules. These microarrays are founded on the primary structure of DNA. By comparison, novel microarrays have been developed which use nondenatured, fully intact nucleic acids, with or without protein or drug complexes, resulting in a 3D structure similar to what is found *in vivo* and ready for experimentation.

Engaging the novel nucleic acid-based microarrays presents a greater opportunity to discover and illustrate the remaining alternative molecular biological processes. This approach allows for the study of intact, nondenatured molecules—conventional, alternative, and multistranded nucleic acids.

Novel microarrays and pharmacogenomics can be employed to make significant offerings towards refining cell biology, genetics, molecular biology, molecular pathology, synthesizing/sequencing nucleic acids, deciphering genomes, ascertaining new gene-drug and protein-drug target sites, and accelerating the drug discovery process.

The next generation of nucleic acid microarrays advances into multistranded and alternative DNA, RNA, and plasmid microarrays. These microarrays immobilize intact, unaltered, nondenatured nucleic acids, using different surface chemistries, onto a solid support. It allows for the characterization of nucleic acid structural transitions, and testing drugs for their ability to bind with DNA and RNA under different conditions. The intact nucleic acids can be placed onto the substrate surface directly or synthesized. The nucleic acids include dsDNA, dsRNA, B-DNA, A-DNA, Z-DNA, A-RNA, Z-RNA, cruciforms, DNA-RNA hybrids, parallel-stranded DNA, peptide nucleic acid, locked nucleic acid, triplex DNA, quadruplex DNA, and pentaplex DNA.

The novel microarrays, along with pharmacogenomics, will allow for new technology development focused on enhancing DNA- and RNA-based research. The novel microarray may well play a significant role in drug discovery and future understanding of basic biological processes. These radical approaches, along with conventional pharmacogenomics, will create dynamic strategies that will optimize genomics, proteomics, and epigenetics.

Reference

1. Gagna CE, Lambert WC. Novel multistranded, alternative, plasmid and helical transitional DNA and RNA microarrays: implications for therapeutics. *Pharmacogenomics*. 2009; 10(5):895-914.

Vol. 15 No. 7

www.dddmag.com

DRUG DISCOVERY & DEVELOPMENT

STRATEGIES & TECHNOLOGIES DRIVING DRUG DISCOVERY TO MARKET

Advantage Business Media

July/August 2012

Bringing Stem Cells to the Forefront

Wide ranges of cell lines and even tissues can now be purchased, allowing more time to explore therapeutic applications.

Drug Safety
PREDICTING POTENTIAL CARDIAC EVENTS

Instrumentation
DETECTING POTENTIAL TOXICITY IN MITOCHONDRIA

Informatics
PUBLIC DATA SPURS PROFILING ADVANTAGE

Clinical Trials
TAKING THE 505(B)(2) ROUTE

Genomics & Proteomics
DNA MICROARRAY TECHNOLOGY

FLOW CYTOMETRY ANALYSIS
page 5

www.dddmag.com
www.dddmag.com
www.dddmag.com
www.dddmag.com